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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,468	07/10/2003	Patrick M. Hughes	17549 (AP)	3251

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,468	HUGHES ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-17 and 21-31* is/are pending in the application.

4a) Of the above claim(s) *26-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-17 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Newly submitted claims 26-31 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The methods of lowering the ratio of an ester prodrug to active drug as found in claims 26-31 do not require the use of retinoids as required in the claims previously under examination. Also, the methods of claims 26-31 are distinct in that claim 26 (the independent claim) does not require any type of therapeutic benefit to treat any disease or condition. As written, claim 26 is simply a vaguely described method, lacking any active steps, for altering a ratio of an ester prodrug to an active drug. There is no actual benefit or effect specified. As such, this appears to be a claim drawn only to the action of altering this ratio.

Note that for the purposes of examination, claim 31 is dependent on non-existent claim 36, and this is taken to be a typographical error. It is assumed this claim is dependent upon newly added claim 26 and will be included with the claims drawn to a distinct invention here.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 26-31 are hereby withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-17, and 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of sustained delivery or a method of treating a disease or condition wherein the retinoid active drug is tazarotenic acid and the ester prodrug is tazarotene, does not reasonably provide enablement for other retinoids wherein the active drug is more than about 10 times as active as the prodrug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In re Wands, set forth the following eight factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph:

1) the quantity of experimentation necessary
2) the amount of direction or guidance provided
3) the presence or absence of working examples
4) the nature of the invention

5) the state of the art
6) the relative skill of those in the art
7) the predictability of the art and
8) the breadth of the claim

Applicant is claiming (in claim 1) any retinoid that will be more than 10 times as active as the prodrug when the specification only shows at page 15, lines 12-21 that tazarotenic acid and tazarotene function in this manner. The specification at page 15 clearly establishes via K_d values that tazarotene is a prodrug of tazarotenic acid and that the tazarotenic acid form (the active drug) is more than about 10 times as active as the prodrug. The citation mentioned above is the only example given which demonstrates this 10 fold activity relationship between a retinoid prodrug and the active form.

Case in point is elucidated by Rephaeli et al. [Drug Development Research 50:379-391 (2000)]. In this article, synthesis and testing of various anti-cancer ester prodrugs yielded different and unpredictable activities when tested in vitro and in vivo. See the discussion at pages 382-383, Tables 1-4. Even compounds of similar structure yielded highly variable activities. Compare, for example compound AN-9 (pivaloyloxymethyl butyrate) versus AN-36 (pivaloyloxymethyl propionate) where AN-9 releases one equivalent of active drug, while AN-36 does not release the active drug BA upon hydrolysis. As discussed in the second column, third full paragraph on page 382, AN-9 when compared to the active drug, the prodrug is found to be

actually "far more effective than the BA." By contrast, the highly similar AN-36 does not function at all to release the active drug. Consequently, it is unclear when designing prodrugs whether the prodrug will have greater activity, less activity or no activity versus the active drug. In the instant application there is disclosed only one ester prodrug, Tazarotene, which is demonstrated to have more than 10 times activity as the active drug tazarotenic acid. Given the unpredictability of designing ester prodrugs that meet the limitations of the claimed invention, it would require undue experimentation to practice the invention as claimed for the active drug is a retinoid that is more than about 10 times as active as the prodrug.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7-9, 12, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilkin, J. (Wilkin ,J. (Allergan, Inc. Avage (tazarotene) cream, 0.1% Irvine California 92612, USA (2002), printed pages 1-17, especially page 1) (already made of record in previous action).

Wilkin teaches Tazarotene for use in treating fine wrinkling, facial mottled hypo- and hyperpigmentation and benign facial lentigines. See the second paragraph under Clinical Pharmacology. Tazarotene is a retinoid prodrug that converts to its active form tazarotenic acid. See the first paragraph under Clinical Pharmacology. Application of the drug is once a day. It is

obvious that fine wrinkling will occur in the periocular or peribulbar region, hence the use of the Tazarotene around the eye to some extent would be obvious when the product is used.

Applicant claims a method of sustained-delivery of a retinoid to treat a disease condition that can be treated by the retinoid. The retinoid ester prodrug is administered periocularly as an ester prodrug that converts to the active retinoid. Regarding the limitation of "sustained delivery" it is noted that the specification at page 8, lines 23-30, that delivery to the periocular space will result in "sustained delivery of the drug to the back of the eye…" Regarding the claim limitation of delivery of the active drug to the posterior part of the eye, it is understood that application of the retinoid prodrug to treat fine wrinkles in the manner of the prior art would obviously perform this function. In this regard, the claims do not require that the disease actually be a disease of the eye. There is a disconnection between the disease and the treatment. As such, the prior art renders obvious the claimed invention. Regarding claim 15, the term "peribulbar" can be defined to mean the area around the eye and does not necessarily mean within the eye itself.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY E. BETTON whose telephone number is (571)272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617